Research Article

Crystal Structure and Molecular Mechanics Modelling of 2-(4-Amino-3-benzyl-2-thioxo-2,3-dihydrothiazol-5-yl)benzoxazole

Ahmed F. Mabied,¹ Elsayed M. Shalaby,¹ Hamdia A. Zayed,²
Esmat El-Kholy,¹ and Ibrahim S. A. Farag¹

¹ Crystallography Laboratory, Physics Division, National Research Centre, Dokki, Giza 12622, Egypt

² Physics Department, Women's College, Ain Shams University, Cairo 11757, Egypt

Correspondence should be addressed to Ahmed F. Mabied; mabied@xrdlab-nrc-eg.org

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The crystal structure of the title compound, 2-(4-amino-3-benzyl-2-thioxo-2,3-dihydrothiazol-5-yl)benzoxazole, was determined. The crystal has P1 space group and triclinic system with unit cell parameters $a = 5.174(3)$, $b = 6.411(6)$, $c = 12.369(10)$, $\alpha = 86.021(4)^\circ$, $\beta = 84.384(5)^\circ$, and $\gamma = 77.191(5)^\circ$. The structure consists of benzoxazole group connected with benzyl via thiazole (attached with amino and thione). Benzoxazole and thiazole rings are almost planar (maximum deviation at C1, $-0.013(3)$, and C10, $0.0041(3)$, resp.). The phenyl ring is nearly perpendicular to both thiazole and benzoxazole rings. A network of intermolecular hydrogen bonds and intermolecular interactions stabilizes the structure, forming parallel layers. The molecular geometry obtained using single crystal analysis is discussed along with results of the molecular mechanics modeling (MM), and the results showed the same *cis* conformation between benzoxazole nitrogen atom and the amino group.

1. Introduction

Organic compounds natural or synthetic are the main source of medical agents and drugs, so knowledge of their molecular structure and conformation is important because it has a direct correlation with their activity. Among of bioactive organic compounds are benzoxazole derivatives; previous reports revealed that substituted benzoxazoles possess diverse chemotherapeutic activities including antibiotic, antimicrobial, antiviral, topoisomerase inhibitors, and anti-tumor activities [1–3]. Benzoxazoles possess the structural isosteres of natural nucleotides (such as adenine and guanine) which allow them to interact easily with the biopolymers of living systems and different kinds of biological activity can be obtained [4]. Benzoxazoles are widely used in industry, among them 2-phenylbenzoxazoles used as organic brightening laser dyes. Other industrial applications were reported, such as dopants in organic light-emitting diodes, chromophores, and chemosensors [5, 6].

Molecular mechanics calculations are an efficient tool and an important aspect of molecular modeling, used for

predicting structure and energy of molecules and heats of formation and used to compare different conformations of the same molecule, further reading in [7, 8].

As reported previously, knowing the structure and conformation of 2-substituted benzoxazole derivatives gives important information for predicting their mode of orientation on the receptor [1]. So, more bioactive drugs in the pharmaceutical industry can be designed. As a result this provides the pharmaceutical community with useful information which may help in the design of more active drugs or other applicable compounds. Herein, we report the crystal structure and conformation of 2-(4-amino-3-benzyl-2-thioxo-2,3-dihydrothiazol-5-yl)benzoxazole, comparing the results with its molecular mechanics modelling.

2. Materials and Methods

2.1. Synthesis. The title compound was prepared according to literature [1] (Scheme 1); melting points were determined in

SCHEME 1: Chemical diagram of synthesis of the title compound.

open-glass capillaries on a Gallenkamp melting point apparatus and were uncorrected. The IR spectra were recorded using KBr discs on a Perkin-Elmer 1430 spectrophotometer.

A mixture of 2 cyanomethylbenzoxazole (1.58 g, 10 mmole), finely divided sulphur (0.32 g, 10 mmole), and triethylamine (1.4 mL, 10 mmole) in absolute ethanol (15 mL) was stirred at room temperature for 30 minutes. Benzyl isothiocyanate (10 mmole) was gradually added and stirring was continued for 1 hour during which a yellowish green crystalline product separated out. The separated product was filtered, washed with ether, dried, and crystallized from dioxane. IR of 2-(4-amino-3-benzyl-2-thioxo-2,3-dihydrothiazol-5-yl)benzoxazole ($\nu \text{ cm}^{-1}$): 3352–3157 (br.NH₂); 1628–1625, 1555–1552, 1451–1450 (C=N, NH bending, C=C); 1340–1326 (C=S), 1248–1242, 1229–1223, 1023–1015 (C–O–C, C–S–C).

2.2. X-Ray Single Crystal Diffraction. The selected crystal was mounted on an Enraf-Nonius 590 Kappa CCD single crystal diffractometer at National Research Center of Egypt [9]. X-ray diffraction data were collected at room temperature with graphite monochromated Mo-K α ($\lambda = 0.71073 \text{ \AA}$) radiation [10]. Refinement and data reduction were carried using Denzo and Scalepak programs [11]. The crystal structure was solved by direct method using SIR92 program [12] which revealed the positions of all nonhydrogen atoms and refined by the full matrix least squares refinement based on F^2 using maXus and CRYSTALS packages [13, 14]. The anisotropic displacement parameters of all nonhydrogen atoms were refined; then, the hydrogen atoms were introduced as a riding model with C–H = 0.95 Å and refined isotropically. The Flack parameter of the absolute structure was refined [15]. The molecular graphics were prepared using ORTEP-3 for Windows [16], DIAMOND [17], and Qmol [18] programs; crystal data is listed in Table 1. The crystallographic information file (CIF) of the title compound is supplementary material, available online (<http://dx.doi.org/10.1155/2014/938360>), and has been deposited (CCDC 675941) at the Cambridge Crystallographic Data Center.

2.3. Molecular Mechanics Modeling. Molecular mechanics *in vacuo* calculations were performed through the HyperChem package [19]. The molecular mechanics (MM⁺) force field was used as it is developed principally for organic molecules [8, 20, 21]. The process of energy minimization was carried out by steepest descents method. The conformational energy of the molecule was calculated.

FIGURE 1: The 50% probability displacement ellipsoids representation of the title compound.

TABLE 1: Crystal data of the title compound.

Crystal Data	
Chemical formula, M_r	$\text{C}_{17}\text{H}_{12}\text{N}_3\text{OS}_2$, 339.44
Crystal system, space group	Triclinic, P1
a, b, c (Å)	5.174(3), 6.411(6), 12.369(1)
α, β, γ (°)	86.021(4), 84.384(5), 77.191(5)
V (Å ³), D_x (mg m ⁻³), Z	397.68(5), 1.417, 1
μ (mm ⁻¹), Temperature	0.34 mm ⁻¹ , 298
θ (°), $F(000)$	3–27, 176
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.030, 0.073, 1
Number of reflections, parameters, and restraints	1644, 209, 0
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å ⁻³)	0.15, -0.14
Absolute structure parameter (Flack)	0.53(2)

3. Results and Discussions

3.1. Crystal Structure Description. Figure 1 shows the molecular structure of the compound as 50% probability displacement ellipsoids diagram. The structure consists mainly of benzoxazole group connected with benzyl via thiazole (attached with amino and thione) at C₇. The compound in general has not planar configuration, where the phenyl ring is nearly perpendicular to both thiazole and benzoxazole rings. However, benzoxazole, thiazole, and phenyl rings are almost planar with the maximum deviation corresponding

FIGURE 2: A view of the molecular packing of the title compound. The $\text{N-H}\cdots\text{S}$ and $\pi\cdots\text{Cg}$ interactions are shown as green and red dashed lines, respectively.

TABLE 2: Hydrogen bond and $\pi\cdots\text{Cg}$ interaction geometry of the title compound, where Cg is the centroid of the C12–C17 ring.

		Length (Å)		Angle (°)
D–H $\cdots$ A	D–H	H $\cdots$ A	D $\cdots$ A	D–H $\cdots$ A
N1–H1 $\cdots$ S2 ⁱ	0.95	2.63 (1)	3.397 (3)	138
Y–X $\cdots$ Cg		X $\cdots$ Cg	Y $\cdots$ Cg	Y–X $\cdots$ Cg
C10–S2 $\cdots$ Cg ⁱⁱ		3.721 (2)	5.264 (3)	153.35 (1)

Symmetry codes: ⁱ $1 + x, -1 + y, z$; ⁱⁱ $-1 + X, 1 + Y, Z$.

to the C1, $-0.013(3)$ Å, C10, $0.0041(3)$ Å, and C15, $0.010(4)$ Å, respectively. The geometrical parameters of the present benzoxazole derivative are in a good agreement with the reported structures which have the same moiety, such as 2-(4-aminophenyl)-1,3-benzoxazole [22] and 2-amino-5-chloro-1,3-benzoxazole [23]. The amino group has *cis* conformation with nitrogen atom of benzoxazole; such information would give an interpretation for its mode of orientation on the receptor [1]. The crystal packing shows a network of intermolecular hydrogen bonds, $\text{N-H}\cdots\text{S}$, and $\pi\cdots\pi$ interactions between S2 atom and the gravity center (Cg) of the phenyl ring (C12–C17), and such intermolecular contacts and interactions stabilize the structure, forming parallel layers as shown in Figure 2 and Table 2.

3.2. Molecular Mechanics Modeling. Figure 3 represents the obtained molecular structure of the title compound using molecular mechanics modeling, and also comparison with that obtained crystallographically is given in Figure 4. The minimum energy structure obtained *in vacuo* by molecular mechanics calculations of the investigated compound does

FIGURE 3: The moleculargraphic of the title compound as obtained by molecular mechanics modelling.

FIGURE 4: The X-ray crystal structure (green) and the obtained theoretically (red) of the title compound.

not match well with the crystal structure obtained experimentally. The global energy minimum conformations as calculated by molecular mechanics *in vacuo* are in agreement with the above-mentioned crystallographically observed *cis* conformations between benzoxazole nitrogen and amino group.

TABLE 3: Selected geometrical values of the experimentally and molecular mechanics obtained structures of the title compound.

Bond angles (°)	EXP.	MM.	Bond length (Å)	EXP.	MM.
C8–S1–C10	92.35 (2)	94.2	S2–C10	1.67 (3)	1.70
C6–C5–C4	116.3 (5)	117.5	C9–N3	1.38 (4)	1.41
C12–C17–C16	120.5 (3)	120.4	C8–C7	1.42 (4)	1.463
N3–C9–N1	121.4 (3)	121.5	C7–O1	1.37 (4)	1.37
C8–C7–O1–C1	179.8 (3)	176.6	C1–C6	1.38 (5)	1.395
S1–C8–C7–O1	0.091 (4)	20.6	N3–C11	1.46 (4)	1.46
C8–S1–C10–S2	177.1 (2)	145.6	C11–C12	1.511 (4)	1.516
N2–C1–C6–C5	179.5 (5)	178.1	N2–C7	1.30 (8)	1.298
C5–C6–O1–C7	178.3 (7)	176.7	N3–C10	1.37 (3)	1.43
C7–C8–C9–N3	176.4 (2)	174.5	C9–N1	1.34 (4)	1.41
N3–C11–C12–C17	21.83 (4)	50.74	C6–C5	1.39 (5)	1.400
N3–C11–C12–C13	158.2 (2)	133.36	C1–C2	1.36 (6)	1.400

Table 3 gives the selected values of bond lengths, valence angles, and torsion angles of the compound, which are obtained by molecular mechanics (MM) as well as the X-ray crystallographic results (Exp.). The dimensions of the benzoxazole ring obtained theoretically almost agree with those obtained experimentally with X-ray diffraction. Although, the phenyl ring is perpendicular to both benzoxazole group and thiazole ring, as obtained by X-rays, there is notable difference in the orientation of the phenyl ring, the phenyl ring. This can be noticed from the values of N3C11C12C17 and N3C11C12C13 torsion angles for the experimental and theoretical results, as shown in Figure 4 and Table 3. This difference can be interpreted as a result of the intermolecular interaction ($\pi \cdots \text{Cg}$), which has been found between the phenyl ring and S2 atom, as shown in Figure 2.

The calculated energy of the experimental and theoretical structures is 140 and 50 kcal·mol^{−1}, respectively. This variation may be due to the experimental structure of the investigated compounds in crystal conditions; that is, the neighbouring molecules, hydrogen bonding, and other nonbonded interactions in the crystal lattice environment are taken into account, in agreement with what was reported in literature showing that the effects of hydrogen-bonding and van der Waals interactions in the crystal structure cause the molecules to adopt higher energy conformations, which correspond to local minima in the molecular potential energy surface [24]. Also, in consent with the notation, which states that the crystallographically observed molecular architecture is a local energy minimum in the absence of its crystal lattice environment [25].

4. Conclusions

The molecular structure of 2-(4-amino-3-benzyl-2-thioxo-2,3-dihydrothiazol-5-yl)benzoxazole was determined using X-ray single crystal technique and molecular mechanics modeling, in order to add useful information for designing new potent drugs. The results obtained from X-ray and molecular mechanics calculations showed the same general nonplanar features of the compound; also the same *cis* conformation between benzoxazole nitrogen and amino was found.

However, there is notable difference at the orientation of the phenyl ring which maybe comes from the intermolecular interactions in the crystal lattice packing, which cause the molecules to be in a higher energy conformation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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